

The University of Chicago

STUDIES TOWARD THE SYNTHESIS OF
4-METHYL-5, 5-DIETHYLURACIL

A DISSERTATION SUBMITTED TO THE FACULTY
OF THE DIVISION OF THE PHYSICAL SCIENCES
IN CANDIDACY FOR THE DEGREE OF DOCTOR
OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

1936

By
REX EVERETT LIDOV

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The writer thanks Dr. Julius Stieglitz most sincerely for his ever ready guidance. His never failing interest and quiet encouragement were sources of inspiration which will always be gratefully remembered.

STUDIES TOWARD THE SYNTHESIS OF
4-METHYL-5,5-DIETHYLURACIL

Ring derivatives of acetoacetic ester with derivatives of phenylhydrazine have for a long time been used in medicine as analgesics and antipyretics. Another series of nitrogenous ring derivatives of acetoacetic ester are the ureides or uracils. These are analogous to barbituric acid, the ureide of the malonic ester series. Since the 5,5-dialkylated, and aryl alkyl barbiturates belong to the most effective hypnotics chemistry has provided, the preparation of the corresponding 5,5-dialkyl and alkyl aryl uracils was attempted, in order that they might be investigated as to any possible hypnotic or other therapeutic properties they might possess.

In a series of synthetic efforts to prepare a 4-methyl-5,5-dialkyluracil, it became evident that the ureide syntheses which yielded excellent results in the preparation of the barbiturates and of 4-methyl-5-ethyluracil did not prove successful in the case of the dialkylacetoacetic esters.¹ The alkylation of the pyrimidine ring has been extensively studied by Johnson and others and it is well known that groups cannot be introduced into the 5 position by any of the alkylation procedures commonly used.² In the light of these facts a new method of attack on the synthe-

¹W. L. Terre, Master's Dissertation, University of Chicago, (1932).

²E. R. Tweedie, Doctor's Dissertation, University of Chicago, (1935). Cf. references in footnotes, p. 16.

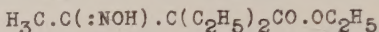
Behrend, *et. al.*, *Ann.*, 229, 5 (1885); *Ann.*, 353, 242 (1907); *Ann.*, 422, 83 (1921).

sis of the desired pyrimidine had to be developed.

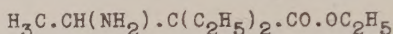
In the present investigation three further series of attempts to build a pyrimidine ring around 2,2-diethylacetoacetic acid will be described. Unfortunately none of the three attained the goal set.

The approach first planned for the synthesis involved the following reaction series:

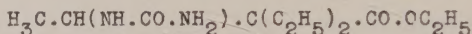
- a. The preparation of ethyl 2,2-diethyl-3-oximinobutyrate,



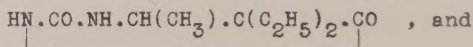
- b. The reduction of the oxime to ethyl 2,2-diethyl-3-amino-butyrate



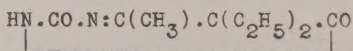
- c. The formation, thru the action of cyanic acid, of ethyl 2,2-diethyl-3-ureidobutyrate,



- d. Ring closure, thru the loss of ethyl alcohol,



- e. Introduction of the double bond by oxidizing the ring compound obtained in (d). The end product would have been the desired 4-methyl-5,5-diethyluracil.

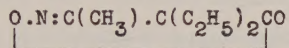


It was anticipated that the final oxidation might be difficult, but it appeared, for the most part, to be a logical plan of attack. The starting material was ethyl 2,2-diethylacetoacetate which can readily be prepared from ethyl 2-ethylacetoacetate, which is itself obtained with even greater ease from ethyl acetoacetate.¹ In the hope that the ethyl 2,2-diethylacetoacetate re-

¹An improved method devised by E. W. Lowe in this laboratory (unpublished work) was used.

quired might be prepared in one step directly from ethyl acetoacetate, the methods of Michael and Barnett were briefly investigated.¹ In the hands of the writer, however, neither of the latter methods yielded results as satisfactory as the two-step process of Lowe.

The oxime of ethyl 2,2-diethylacetoacetate was first prepared by Betti in 1898.² It was attempted to repeat his work; highly variable results were obtained with yields never exceeding five per cent of the theoretical quantity of oxime. In some cases the product obtained was an altogether different solid, melting seventeen degrees lower than the oxime (m.p. 56°-57°). It was identified by analysis as 3-methyl-4,4-diethylisoxazol-5-one:



The factors responsible for the condensation of the oxime to the isoxazolone, in the experiments supposedly leading to the oxime itself, were not determined, but it was soon learned that in alkaline solution this condensation was favored. A similar fact had been reported by Billon with respect to the formation of 3-methyl-4,4-dimethylisoxazol-5-one.³

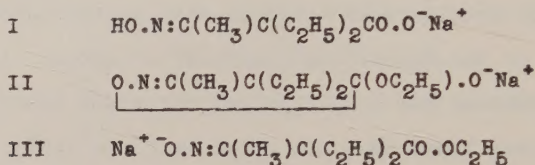
In order to improve the yield of oxime the action of a concentrated solution of hydroxylamine in ethanol (95 per cent) was studied. The first solution prepared contained an excess of sodium ethoxide. This, it was later learned, was caused by incomplete reaction between the hydroxylamine hydrochloride, present partly in solid form, and the sodium ethoxide solution. When

¹Michael, J. Pr. Chem., 72, 554 (1905); Barnett, Ann., 186, 188 (1877).

²Betti, Gazz. Chim. Ital. (I), 28, 274 (1898).

³P. Billon, Ann. Chim. (10), 7, 356 (1927).

the ethyl 2,2-diethylacetoacetate was treated with the solution of hydroxylamine containing sodium ethoxide a white solid was immediately precipitated. This solid, insoluble in both alcohol and water, was easily shown to contain sodium, and to give very good yields of the isoxazolone with dilute mineral acids at 0° . These facts indicated that the precipitate is a salt of one of the following structures:



On the basis of its nitrogen content, the first of the formulae written is assigned to the salt. (See p. 17.) The reaction thus led to a good preparative method for the formation of the isoxazolone.

While this part of the investigation was being prosecuted, the results of some other work, carried on simultaneously, made it seem wise to drop the attack thru the oxime. Hence, the study of the action of sodium ethoxide-free solutions of hydroxylamine on the ketone was not carried on.

Billon had observed that methyl dimethylisoxazolone could be converted into 2,2-dimethyl-3-oximinobutyramide thru the action of concentrated ammonium hydroxide.¹ It was found that the new methyldiethylisoxazolone could not be ammonolyzed in this fashion. This is quite in accord with the general differences found in the hydrolysis of the dialkylated acetoacetic esters. While the dimethyl esters are quite readily attacked by alkali, the diethyl esters, and in general, the di-"higher alkyl" esters are quite

¹Ibid.

impervious to its action, no doubt as the result of stereochemical interferences.¹ The diethyl isoxazolone was found to be stable toward liquid ammonia even in the presence of ammonium chloride (i.e. in acid solution), and toward ammonia gas at elevated temperatures.

Later it was found, in this investigation, that the oxime of ethyl 2,2-diethylacetoacetate could be prepared with consistent yields of fifty per cent of the theoretical if a mixed solvent of alcohol and water is used in the preparation of the oxime by a modified method of Betti. So far as has at present been determined this is the best method for preparing the ethyl 2,2-diethyl-3-oximinobutyrate.

The attempt to reduce the oxime to ethyl 2,2-diethyl-3-aminobutyrate was unsuccessful. Billon had prepared ethyl 2,2-diethyl-3-oximinobutyrate in order to reduce it to 2,2-diethyl-3-aminobutan-1-ol. He was able to show that some ethyl 2,2-diethyl-3-aminobutyrate could be isolated from his reaction mixture,² but only in very small quantities. The reducing agent employed by him was metallic sodium in hot ethyl alcohol. It appeared wise to search for some reducing agent which would attack the oxime group and yet be insufficiently strong to reduce the carbethoxy group. Sodium amalgam seemed best suited for the purpose. It was found, however, that it was not sufficiently powerful, under the conditions of the experiment, to attack even the oxime group.

It was decided to abandon this phase of the investigation in favor of a more direct attempt to prepare ethyl 2,2-diethyl-3-aminobutyrate. The latter substance should combine as well with cyanic acid as the amine would; by this step the necessity for re-

¹Michael, Ber., 38, 2096 (1905).

²P. Billon, op. cit., p. 362.

oxidizing the $-CH.NH-$ group to a $-C:N-$ group, after the ring had been closed, would be eliminated.

Two methods of procedure seemed to be available for the preparation of the imino compound. First, the direct introduction of the imino group thru the action of ammonia on ethyl 2,2-diethyl-acetoacetate, and second, the alkylation of ethyl 2-ethyl-3-imino-butyrate. H. Meyer attempted the first of these methods, but he met with no success.¹ He had first found that the mono alkyl derivative, ethyl 2-ethylacetoacetate would, when treated with four or five volumes of concentrated ammonium hydroxide, form 33 per cent of the theoretical quantity of the desired ethyl 2-ethyl-3-iminobutyrate. If greater quantities of ammonium hydroxide were used, then, according to Meyer, the formation of 2-ethylacetoacetamid was favored. In repeating this work during the course of this study, it was found that the actual volume of ammonium hydroxide employed is immaterial - in any case there were obtained 33 per cent of the imine, 33 per cent of the amide and 33 per cent of the unchanged ester. Meyer's conclusions regarding the lack of activity of the diethyl ester toward ammonia were completely confirmed. It was further shown that increasing the concentration of ammonia and the use of shaking apparatus to insure better contact, than he had achieved, between the oil and the aqueous phases of the system led to the same negative results.

The alkylation of ethyl 2-ethyl-3-iminobutyrate had not previously been attempted. It seemed wise, before trying the alkylation reaction, to determine whether a more economical conversion of the ketone to the imine, than by the method of Meyer, might be effected.

¹H. Meyer, Monatshefte, 27, 1084-5 (1906).

The assumption was made that in alcohol solution the amide formation, which necessitates the loss of a molecule of alcohol, would be retarded; it was further argued that by reason of this inhibition more of the ketone ester would be available for imine formation, a process which would be favored in non-aqueous solution, inasmuch as it involves the loss of a molecule of water. Experiments completely confirmed this reasoning. It was found that, by the passage of ammonia gas thru a constantly agitated solution of the ester in alcohol over a period of approximately sixty hours, a 66 per cent conversion of the material into the desired imine could be readily accomplished. With an adequate supply of the starting material thus easily obtainable the study of the alkylation was commenced.

The experimental results obtained left no doubt as to the unsuitability of the usual alkylating methods employed in the acetoacetic ester series for this specific reaction. When the imine was treated with ethyl iodide in an alcoholic solution of sodium ethoxide only diethyl ether was formed, and the imine was recovered unchanged. This result may be readily understood if the tautomerization of the imino derivative leads, as it most likely does, to ethyl 2-ethyl-3-aminocrotonate, $\text{H}_3\text{C}.\text{C}(\text{NH}_2):\text{C}(\text{C}_2\text{H}_5)\text{CO}.\text{OC}_2\text{H}_5$, which would be basic and certainly less acidic than alcohol itself. With the basic imino group present, the two other tautomeric forms, the imino ester itself, and $\text{CH}_3\text{C}(:\text{NH}).\text{C}(\text{C}_2\text{H}_5):\text{C}(\text{OH})(\text{OC}_2\text{H}_5)$ would also, presumably, be weaker acids than alcohol. As a result, in alcoholic solution the sodium ethoxide would be the chief sodium salt present.

Many attempts to effect the formation of a potassium salt of the imine thru the use of potassium amid in liquid ammonia solution were made. The results of these reactions were not, how-

ever, clear cut. The reactions moreover, required much time, and very rigorous control of the experimental conditions. Liquid ammonia was therefore abandoned in favor of a more direct method of procedure.

When ethyl 2-ethyl-3-iminobutyrate is dissolved in an inert solvent (ether or benzene) and treated with powdered sodium, or better still, with potassium, the metal readily goes into solution with the evolution of hydrogen gas. The product of this reaction was treated with ethyl iodide, and the material so obtained fractionated in a high vacuum line after the solvent had been evaporated. The fractionation division points were wholly arbitrary but the results showed clearly that alkylation had been successfully attained. Indeed, the alkylation was more thorough than was actually desired; the analysis showed that ethyl 2,2-diethyl-3-ethyliminobutyrate had been formed. This was confirmed by the chemical behaviour of the substance.

While it is entirely possible that the ethylimino group which had been formed during the course of the alkylation might be replaced by an imino or by a ureido group (using urea, thiourea, isourea, etc.), such an attempt was not made; it appeared a wiser policy to try to prevent the nitrogen ethylation from taking place. Theoretically, this might be achieved by blocking the nitrogen with a benzoyl group which could subsequently be ammonolyzed off. Ethyl 2-ethyl-3-benzoyliminobutyrate was therefore prepared. However, since the study of the alkylation of this compound gave promise of requiring an extended period of time it was decided to leave it for the time being in order to prosecute more actively an attack on the problem of the formation of the pyrimidine ring thru ethylacetoacetamid, which was being simultaneously carried on, and which seemed to show the possibility of more im-

mediate results. With this decision the work went into its third phase.

Unlike the alkylation of the imino ester, which presents a problem of considerable difficulty, the alkylation of 2-ethyl-acetoacetamide is completely straightforward. The substance was alkylated by H. Meyer and 2,2-diethylacetoacetamide was formed.¹ Meyer, however, failed to show that the ethyl group had become attached to the carbon, and not to the nitrogen atom. The carbylamine test, applied to the acid hydrolysis product of the compound prepared by Meyer's method, left no doubt that he had actually obtained the 2,2-diethylacetoacetamide.

With the view of testing the possibilities of converting the acid amide into a ureide, 2,2-diethylacetoacetamide was combined at 100° with phenyl isocyanate, to form N-2,2-diethylacetoacetyl-N'-phenylurea, $H_3C.CO.C(C_2H_5)_2.CO.NH.CO.NH.C_6H_5$. Such a urea, non-phenylated, should be convertible into the desired pyrimidine. A series of experiments was therefore commenced to determine how acid amides might be converted into the corresponding ureids. Two reactions were studied.

Nitro-urea under the influence of dilute alkali, or dry under the influence of heat, breaks down in the following manner:



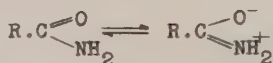
The cyanic acid liberated might react with an acid amide to form a substituted urea. The reaction is one which goes very readily with amines,² but apparently not at all with the amides. In alcohol solution ethyl allophanate was formed by the reaction of the cyanic acid with the solvent alcohol. In the absence of sol-

¹H. Meyer, Monatshefte, 28, 2 (1907).

²Davis and Blanchard, J. Am. Chem. Soc., 51, 1790 (1929).
J. S. Buck and C. W. Terry, J. Am. Chem. Soc., 58, 854 (1936).

vent, cyanuric acid was the only product. It was found necessary to add small amounts of alkali to the reactions carried out in alcohol solution in order to obtain the necessary decomposition of the urea. The amides are not sufficiently alkaline in reaction to induce this breakdown. There was the possibility that the alkali in solution might serve to activate the amid to some extent. None of the experimental evidence indicated that such activation occurred. In order to conserve the 2,2-diethylacetoacetamide some of these test reactions were carried out with acetamide.

Diethylacetoacetamid was refluxed with a concentrated solution of potassium cyanate.¹ Again the results were completely negative. The probability exists that in an acid amide internal salt formation occurs:



If this is the case, then the amide might well be expected not to react with cyanic acid. However, when such a substance is treated with potassium cyanate the potassium ion neutralizing the acid amide would form $\text{R.C}(\text{:NH})\text{O}^-\text{K}^+$ which might be expected to leave the amide group free to react with the cyanate ion or with the cyanic acid formed in the solution by the hydrolysis of the salt. This, indeed was the situation which confronted Baeyer in the action of potassium cyanate on uramil. In the present instance, however, internal salt formation is apparently not the important factor in preventing the amide from reacting with cyanic acid.

While these attempts to use the amide as a building stone in the synthesis of the desired uracil have failed, the way is still open for at least two other attempts. One possible road lies

¹Cf. von Baeyer, Ann., 127, 3 (1863) on the formation of pseudouric acid.

thru the formation of an imino ester: $\text{CH}_3\text{CO.C}(\text{C}_2\text{H}_5)_2\text{C:NH}(\text{OC}_2\text{H}_5)$. The basic imino ester group should react quite readily with nitro-urea or with cyanic acid. This line of investigation has been undertaken by Mr. Glenn Simmons under the direction of Dr. J. Stieglitz.

The other possibility lies in the formation of carboben-zoxy isocyanate. This compound is not yet known, but its prepara-tion should be possible without excessive difficulty. It would permit the use of conditions identical with those which success-fully led to the formation of N-2,2-diethylacetoacetyl-N'-phenyl-urea, thus leading to the formation of N-2,2-diethylacetoacetyl-N'-carbobenzoxymurea. The removal of the carboben-zoxy group, per-haps by hydrogen and platinum black,¹ should then yield the de-sired urea.

In addition to the above attempts to build the urea group onto the 2,2-diethylacetoacetic acid chain the reactions of ethyl 2,2-diethylacetoacetate and ethyl 2,2-diethyl-3-oximinobutyrate with ethylisourea were studied. It was hoped that a straightfor-ward condensation would be obtained, yielding the desired ethoxy-pyrimidine. The results were negative. The experiments do not require any detailed discussion: the conditions employed will be adequately described in the experimental part of this disserta-tion.

Despite the fact that the above attempts to synthesize 4-methyl-5,5-diethyluracil have all led to negative results, the way to the preparation of the compound is far from completely closed. The methods of attack employed were, when this investigation was commenced, altogether new with respect to this problem, and there

¹Bergmann and Zervas, Ber., 65, 1200 (1932).

was no indication as to which of the synthetic tools used would prove most effective. Thus, despite an intense desire to reach the goal set, the investigation was of necessity to a large extent exploratory. Whenever, in the course of this work, progress seemed excessively slow, and some other method of procedure appeared to promise more rapid results, the slow method was put aside in order that the one which promised to be more rapid might be more intensively studied.

Two methods of procedure thru the use of diethylacetoacetamid have been suggested; there remains the possibility of converting the newly prepared ethyl 2,2-diethyl-3-ethyliminobutyrate into the desired ureide, and the possibility of preparing ethyl 2,2-diethyl-3-iminobutyrate by alkylating ethyl 2-ethyl-3-benzoyliminobutyrate. Should the latter alkylation succeed, the removal of the benzoyl group by ammonolysis in liquid ammonia solution should not prove too difficult a task. Should these methods all fail the more intensive study of the reduction of ethyl 2,2-diethyl-3-oximino butyrate to ethyl 2,2-diethyl-3-aminobutyrate appears to be indicated. This method of preparation now, however, seems the most arduous and least promising of the group suggested.

Experimental Part

1. Preparation of ethyl 2-ethylacetoacetate.--The method employed is essentially the modification used by Dr. E. W. Lowe in this laboratory.¹ In a one-liter round-bottom flask fitted with a reflux condenser, 250 g. of ethyl alcohol, distilled from sodium ethoxide, was treated with 23 g. (1 mole) of sodium, added slowly over a period of half an hour. As soon as the sodium had dissolved completely, 130 g. (1 mole) of ethyl acetoacetate was rapidly added to the solution thru the reflux condenser. With the addition of the ester, a large quantity of heat is liberated and the solution assumes a light yellow color. Immediately following the addition of the ester, the introduction of ethyl bromide (109 g. 1 mole) was begun. The latter was added at such a rate that the solution continued to reflux gently thru-out the entire addition period. It is imperative that the addition be sufficiently slow to keep the reaction continually under control. Sodium bromide began to precipitate when approximately half of the ethyl bromide had been added. After all of the reagent had been introduced the mixture was refluxed over a steam bath for two hours. Following this the reflux condenser was removed and most of the alcohol permitted to evaporate off. Sufficient water was then added to the residue to dissolve all of the sodium bromide, and the aqueous phase was separated from the oil by means of a separatory funnel. The aqueous solution was washed three times with small quantities of ether and the ethereal washings were added to the separated esters. The ethereal solution was then washed three times with small quantities of a saturated water solution of sodium chloride in order to remove sodium bromide which had remained dissolved in the oil. The combined aqueous washings were then washed twice with

¹Unpublished work.

ether and the washings added to the ester solution. The ether solution was dried over anhydrous sodium sulfate, filtered, and the ether evaporated from the oil over an electric hot plate. The residual oil was fractionated. An eight ball, air jacketed Snyder column was employed for the fractionation. The fraction boiling at 188° - 194° was collected. A yield of 74-76 per cent of the theoretical was consistently obtained.

It was found best, when this preparation was carried out on a large scale, to employ a three necked flask fitted with a dropping funnel, a reflux condenser, and a mercury seal stirrer. The use of the stirrer greatly reduced the bumping caused by the precipitated sodium bromide.

2. Preparation of ethyl 2,2-diethylacetoacetate.--The method of preparation of this compound is identical with that employed for the mono ethyl derivative. One mole of ethyl 2-ethyl-acetoacetate (158 g.) was used, and the fraction boiling between 208° and 214° collected. The yield varies between 55 and 57 per cent of the theoretical.

3. Preparation of ethyl 2,2-diethyl-3-oximinobutyrate.--

a. The method of Betti.¹ This method, described below, gave highly variable results; in some cases the end product was 3-methyl-4,4-diethylisoxazol-5-one rather than the oxime.

Equi-molecular quantities of sodium carbonate, hydroxylamine hydrochloride and ethyl 2,2-diethylacetoacetate are refluxed in four or five volumes of absolute ethanol over a water bath until carbon dioxide is no longer evolved and the solution has assumed a light yellow color. This ordinarily requires from three to five hours. Water is then added to the mixture and heating is continued until almost all of the alcohol had been removed. Then

¹Op. cit.

sufficient water is added to dissolve all of the salt residues and to separate the solution into two phases. The aqueous phase is separated, washed with ether and the ethereal washings are added to the oil. After the ether is removed an oily residue remains which crystallizes after standing for twenty-four hours.

This procedure was not found to give satisfactory results. In one case more than twenty hours of refluxing was required before the solution showed a yellow color and stopped evolving carbon dioxide. Instead of the desired oxime the reaction product was 3-methyl-4,4-diethylisoxazol-5-one, $\text{O.N:C(CH}_3\text{).C(C}_2\text{H}_5\text{)}_2\text{CO}$. In the majority of cases a yield of less than five per cent of the oxime was obtained; most of the ester was recovered unchanged.

b. The following new procedure, giving consistently good yields of the oxime, was developed.

Ethyl 2,2-diethylacetoacetate (18.5 g., 0.1 mole) was treated with 7 g. (0.15 equiv.) of sodium carbonate and 10.1 g. (0.15 mole) of finely powdered hydroxylamine hydrochloride in a mixed solvent consisting of 15 cc. of water and 75 cc. of ethanol (95%). The mixture was refluxed for approximately three hours; at the end of this time the condenser was removed and the solution reduced to half its volume. The solution was filtered and the filtrate was strongly chilled in an ice and salt bath; chipped ice was added to the solution in order that it might be slowly diluted with water. In this fashion 10 g. of the oxime melting, without recrystallization, at 54° - 55° is obtained, a yield of fifty per cent of the theoretical. The oxime melts, after two or three recrystallizations, at 56° - 57° . The material is best recrystallized by solution in 95 per cent ethanol, chilling of the solution, and precipitation by dilution with ice.

4. Preparation of 3-methyl-4,4-diethylisoxazol-5-one.--

In a flask fitted with a reflux condenser 20.7 g. (0.9 mole) of sodium was dissolved in 150 cc. of 95 per cent ethanol. To the sodium ethoxide solution was added 41.4 g. (0.6 mole) of finely powdered hydroxylamine hydrochloride, and the mixture refluxed for six hours. At the end of this time the mixture was filtered, the filtrate evaporated in vacuo to half its volume, and 55.8 g. (0.3 mole) of ethyl 2,2-diethylacetoacetate was added to the solution. A solid was at once precipitated with the evolution of a large amount of heat. The mixture was refluxed for ten minutes, cooled, and the solid separated by filtration of the solution. The solid was suspended in an equal volume of alcohol and the suspension heated until the alcohol commenced to boil. The mixture was cooled, the separated solid brought on a filter and air dried on the filter. The compound was identified as the sodium salt of 2,2-diethyl-3-oximinobutyric acid. It is a very fine, definitely crystalline powder with a characteristic satin sheen.

The salt was suspended in cold water, and the mixture was maintained at 0° while the salt was decomposed by an excess of molar sulfuric acid. The acid was added dropwise and with vigorous stirring to the suspension until the mixture showed a permanent acid reaction toward litmus. The 2,2-diethyl-3-oximinobutyric acid apparently condenses immediately to the isoxazolone, for with this procedure the isoxazolone was obtained as a well defined, crystalline solid melting sharply, without recrystallization, at 40°-41°. Recrystallization of the compound does not alter the melting point. The yield, 38 g., was 76 per cent of the theoretical.

Analysis: calculated for $C_8H_{13}O_2N$; C, 61.93%; H, 8.38%; N, 9.03%; found; C, 61.83%; H, 8.55%; N, 9.12%, 9.19%.

The nitrogen content of the sodium compound was also deter-

mined: Calculated: for $\text{HO.N:C(CH}_3\text{)C(C}_2\text{H}_5\text{)}_2\text{CO.O}^-\text{Na}^+(\text{C}_8\text{H}_{14}\text{O}_3\text{NNa})$, N, 7.18%; for $\text{O.N:C(CH}_3\text{)C(C}_2\text{H}_5\text{)}_2\text{C(OC}_2\text{H}_5\text{).O}^-\text{Na}^+$, and its isomer, the sodium salt thru the oxime group, $\text{Na}^+\text{O.N:C(CH}_3\text{)C(C}_2\text{H}_5\text{)}_2\text{CO.OC}_2\text{H}_5$, $(\text{C}_{10}\text{H}_{13}\text{O}_3\text{NNa})$, N, 6.28%; found; N, 7.00%, 7.23%. On the basis of these nitrogen determinations the sodium salt is assigned the first of the structural formulae here written.

The filtrate from which the isoxazolone had been separated was concentrated and tested for sodium. A precipitate of sodium pyroantimonate indicated that the alcohol insoluble solid contained sodium.

As the isoxazolone had not been previously reported, its solubilities were determined. It is readily soluble in alcohol, benzene, ether, carbon tetrachloride, chloroform, and liquid ammonia. It is insoluble in water. The solid has a relatively high vapor pressure, and a small sample exposed on a watch glass will disappear in the space of half a week. It can be satisfactorily recrystallized either by the chilling of a warm concentrated alcoholic solution of the compound, or by precipitation with ice from its solution in cold alcohol, after the fashion described for the oxime.

5. Attempted ammonolysis of 3-methyl-4,4-diethylisoxazol-5-one.--

a. An attempt was made to extend the observation of Billon on the ammonolysis of dimethylisoxazolone to the diethylisoxazolone.¹ Billon employed hot aqueous ammonium hydroxide as the ammonolyzing agent, and followed the course of the reaction by observing the solution of the 2,2-dimethyl-3-oximinobutyramide which was formed. Because the latter compound is soluble in hot water and because 2,2-diethylacetoacetamide is also soluble in hot water

¹Op. cit.

it was to be expected that the product of the ammonolysis of the diethylisoxazalone would also be soluble in hot water and that the reaction course could be followed by the solution of the 2,2-diethyl-3-oximinobutyramid formed. However no solution occurred when the diethylisoxazalone was treated with aqueous ammonia; the starting material was recovered unchanged. The experiment was conducted in the following manner.

Methyldiethylisoxazalone (10 g.) was treated at 50° for a period of twelve hours with a concentrated aqueous solution of ammonium hydroxide. A stream of gaseous ammonia was passed thru the mixture thru-out the duration of the experiment. No perceptible change occurred. The solution was then refluxed for thirty-six hours; still no change was observed. Refluxing was discontinued and the solution was maintained in contact with the isoxazalone for an additional six days, during which ammonia gas was constantly bubbled thru the mixture. At the end of this period 9 g. of a solid melting between 39.5° and 40.5° was recovered. A sample of the crystals was mixed with isoxazalone melting at 40°-41°. The mixture melted at 40°-41°. No reaction had taken place.

b. The isoxazalone was dissolved in liquid ammonia, and permitted to remain in solution until the ammonia had completely evaporated. This required about two hours. The isoxazalone was recovered unchanged.

c. That hydrogen ion might catalyze the ammonolysis of the isoxazalone ring was easily possible. The isoxazalone was dissolved in liquid ammonia saturated with ammonium chloride. The solid left after the ammonia had evaporated was extracted with ether. The ether, after evaporating, left a solid residue melting at 40°-41°. All of the isoxazalone was recovered unchanged.

d. The isoxazalone was heated to 150° and ammonia gas was

bubbled thru the melt for a period of three hours. At the end of this time the melt was cooled and it solidified. The isoxazolone was recovered unchanged.

6. Attempted reduction of ethyl 2,2-diethyl-3-oximinobutyrate.--Ethyl 2,2-diethyl-3-oximinobutyrate (5.6 g.) was dissolved in 12 cc. of 95 per cent ethanol to which had been added 3 cc. of water and 2 cc. of glacial acetic acid. To the refluxing solution a 2.5 per cent sodium amalgam (20 g.) was added over a period of two hours. The mercury was removed and the solution heated at reduced pressure until most of the alcohol had distilled off. The solution was then made basic to litmus with sodium carbonate. An oil separated which solidified on cooling. The aqueous mixture was thrice extracted with ether and the ethereal solution dried over a mixture of anhydrous sodium carbonate and anhydrous sodium sulfate. The solution was filtered and the ether evaporated, leaving a solid residue. It melted at 55° - 56° . It was mixed with some of the original oxime melting at 55° - 56° . The melting point of the mixture was not lowered. No reaction had taken place.

The experiment was repeated with five times as much of the amalgam in a more acid solution (100 g. of the amalgam and 50 cc. of glacial acetic acid) but to no avail; the oxime was not attacked.

7. Preparation of ethyl 2-ethyl-3-iminobutyrate.--

a. Ethyl 2-ethylacetoacetate (78 g., 0.5 mole) was introduced into a liter flask and 350 cc. of concentrated ammonium hydroxide was poured over the ester; the two liquids were left together for approximately ten hours.¹ During the course of the ten hour period they were vigorously shaken three or four times. At the end

¹H. Meyer, Monatshefte 27, 1089 (1906).

of that time the two phases were separated, and the aqueous phase was washed three times with small amounts of ether.¹ The ether washings were added to the main body of oil. Air was bubbled thru the solution for a period of about an hour to remove ammonia gas; during this process most of the ether was removed as well as most of the ammonia. The residual oil was then held at 60° in vacuo in order to remove the ether and ammonia it still retained. Following this it was vigorously chilled. In this fashion a total of 29 g. of the imino compound melting at 54°-55° can be obtained. The yield is 33 per cent of the theoretical. Three or four recrystallizations of the solid from alcohol, from which it can be precipitated with ice, raise the melting point to 59°-60°, which is the value recorded in the literature. About 33 per cent of the ethyl 2-ethylacetoacetate is recovered.

b. The following procedure was developed in order that the imino compound might be more economically obtained. Not only is the yield very much improved, but the product is obtained in a much purer state.

Half a mole of ethyl 2-ethylacetoacetate (79 g.) was dissolved in 100 cc. (1.25 volumes) of 95 per cent ethanol and the solution was placed on a shaking machine, and shaken steadily for a period of 60 hours. Ammonia gas was bubbled thru the solution for the entire duration of the shaking period. For the first two hours in which ammonia was introduced into the solution, the temperature of the liquid rose considerably above room temperature, but after the initial period of absorption was over, it dropped again to room temperature. At the end of the sixty hour period the flask was attached to the water aspirator and evacuated; pro-

¹The aqueous phase contains the 2,2-diethylacetoacetamid in solution. The method employed in obtaining the amid from solution is described later on in this dissertation.

vision was made for air to pass thru the solution during the evacuation. This process removed both ammonia and alcohol from the solution. After evacuation had continued for about half an hour a copious precipitate was obtained. The solid was recovered by filtering the solution, and the filtrate was again evacuated. The process of alternate filtration and evacuation was continued until no more solid was obtained. In this fashion 55 g. of ethyl 2-ethyl-3-iminobutyrate melting at 58° - 59° was obtained. This represents a yield of 67 per cent of the theoretical. One crystallization from alcohol suffices to raise the melting point to 59° - 60° .

8. Preparation of ethyl 2-ethyl-3-benzoyliminobutyrate.--

Ethyl 2-ethyl-3-iminobutyrate (10 g.) was suspended in approximately 10 g. of pyridine, and 10 g. (a slight excess) of benzoyl chloride was added to the mixture. With the first addition of benzoyl chloride the suspended solid went into solution, and a large quantity of heat was evolved. With the addition of the remainder of the benzoyl chloride a solid precipitated out. The mixture, after becoming cool, was almost completely solid; it was permitted to stand for twenty-four hours. Water was then added and the suspension was brought onto a filter and the solid recovered. It melted without recrystallization at 74° - 76° and weighed 7 g. After repeated recrystallization from ethanol (70 per cent) the compound melted sharply at 76° - 77° . This represents a yield of 41 per cent of the theoretical.

The pure solid was analyzed for nitrogen by the micro-Dumas method. Calculated for $C_{15}H_{19}O_3N$, N, 5.36%; found; N, 5.18%, 5.24%. This compound has not been previously reported.

9. Attempted preparation of ethyl 2,2-diethyl-3-iminobutyrate.--

a. To 5 cc. of ethyl 2,2-diethylacetoacetate was added 20 cc.

of concentrated ammonium hydroxide. The mixture was placed on a shaking machine and shaken for 48 hours, and then allowed to stand for 60 hours. At the end of this time the two phases were separated. The oil phase was found to be unreacted ethyl 2,2-diethylacetoacetate which was recovered almost quantitatively.

b. To 5 cc. of ethyl 2,2-diethylacetoacetate was added 15 cc. of concentrated ammonium hydroxide. The flask containing the mixture was attached to an ammonia tank and flushed with the gas. It was placed on a shaking machine and shaken for 72 hours. Throughout this period the mixture was under a pressure of ammonia gas of 1,180 mm. of mercury. The starting material was recovered unchanged.

c. The ethylation of ethyl 2-ethyl-3-iminobutyrate was attempted in the usual fashion.

To 30 g. of alcohol distilled from sodium ethoxide was added 1.38 g. (0.06 mole) of sodium. After the sodium had gone completely into solution 10 g. (0.06 mole) of ethyl 2-ethyl-3-iminobutyrate was added to the solution, and following this, 6.5 g. (0.06 mole) of ethyl bromide was introduced. A precipitate was obtained almost immediately. The mixture was permitted to reflux over a steam bath for two and a half hours, and it was then filtered. The filtrate was heated until almost all of the alcohol had been removed. The residual oil solidified as soon as it was chilled. The solid obtained in this manner melted at 54° - 55° . It was extracted with ether in order to separate the organic material from sodium bromide. The ether solution was evaporated to dryness, and the solid recovered was recrystallized from alcohol by precipitation with ice. The recrystallized solid melted at 58° - 59° . Some of the compound was mixed with ethyl 2-ethyl-3-imino butyrate of the same melting point; the melting point of

the mixture was not lowered.

d. Ethylation of the potassium salt of the imino compound prepared in liquid ammonia solution was attempted. The procedure required that water be very rigorously excluded. The experiment was performed under an atmosphere of dry nitrogen.

A three necked 200 cc. round bottom flask fitted with a mercury seal stirrer and a reflux condenser was used for the reaction. The third neck was fitted with a gas delivery tube which reached to the bottom of the flask. The interior of the flask communicated with the atmosphere thru a trap which was filled with liquid ammonia containing sodium in solution. This trap was attached to the reflux condenser. Provision was made to lead dry nitrogen into the system either thru the condenser, or thru the gas delivery tube in the third neck. Under these circumstances, a flow of nitrogen out of the flask could easily be maintained whenever it was necessary to remove the gas delivery tube in order to add reagents to the system; moisture could thus be prevented from entering the flask. Before the reaction was commenced the flask was thoroughly dried by the passing of hot dry nitrogen thru it for a period of about two hours. Liquid ammonia was introduced into the flask by condensation of ammonia gas which was obtained by evaporation of ammonia from a solution of sodium in liquid ammonia. A carbon dioxide snow acetone mixture, placed around the flask, was employed as the condensing agent. The reaction was carried out in the following manner:

To approximately 150 cc. of liquid ammonia was added 4.8 g. (0.12 mole) of potassium metal; an iron-iron oxide catalyst (a small rusty spring) was simultaneously introduced into the solution. It required about an hour for the potassium to be converted into potassium amid, the end of the reaction being determined by

the disappearance of the blue color of the potassium solution. When the potassium had been completely converted into the amid 20 g. (0.12 mole) of ethyl 2-ethyl-3-iminobutyrate was added. After the solution thus obtained was stirred for half an hour, the ammonia was removed by evaporation in a stream of nitrogen. As the ammonia evaporated, a solid precipitated. Whether there were one or two solids present in the precipitate could not be determined. A thermometer was placed in the solid material, and its temperature was raised to ninety degrees. The solid liquified completely. By this procedure any unreacted starting material should have been converted into the potassium salt of the imino compound. Without cooling of the melt an excess of ethyl bromide was added to it. Following the addition of the ethyl bromide 30 cc. of anhydrous ether was added to the reaction mixture which was refluxed for six hours, and then permitted to stand overnight.

The ether solution was filtered and the filtrate set aside. At the end of two hours a solid began to precipitate from the ether solution. It was separated by filtration. The solid, while apparently not gummy, clogged the filter paper, and made the filtration a long and difficult one. The filtrate was freed of ether by evaporation at 40° under a pressure of 15 mm. Removal of the ether left a thick, yellow brown viscous gum. It was placed in vacuo over calcium chloride and high melting paraffine wax (Parawax).

The solid obtained from the ether solution was washed five times with ether by decantation. The insolubility of the substance in ether completely precludes the possibility that it might be either the starting material or the desired product. Nevertheless, a nitrogen determination by the micro-Dumas method was carried out. The results of the analysis were; N, 8.29%, 8.23%.

These values cannot be readily correlated with any product which might be expected from the reaction mixture. Certainly, the solid was not the desired imino compound. It was not further studied.

The material in the desiccator had not crystallized after thirty days in vacuo.

A gum, identical with that described above, had been prepared in a similar previous experiment. An attempt was made at that time to distill the gum under a pressure of one millimeter. The starting material was found to distill at 74° - 76° at 1 mm. No distillate was obtained from the gum until the heating bath temperature was raised above 100° . A colorless liquid then commenced to distill. After about four drops had been collected, the distillation was stopped. The odor of the material was identical with that of ethyl 2,2-diethylacetoacetate. A boiling point determination by the micro method gave the boiling point as 208° ; this is the boiling point of ethyl 2,2-diethylacetoacetate. With this data it seemed certain that the material was being decomposed. It also seemed to indicate that the alkylation had, to some extent, been accomplished. Distillation, even at pressures as low as one millimeter was definitely counter-indicated.

The gum in the desiccator was, therefore, subjected to analysis by the micro-method. The results were: N, 6.78%, 6.75%. These values are very close to those calculated for ethyl 2,2-diethyl-3-ethyliminobutyrate ($\text{CH}_3\text{C}(\text{:NC}_2\text{H}_5).\text{C}(\text{C}_2\text{H}_5)_2\text{CO.OCC}_2\text{H}_5$), for which the calculated value is, N, 6.57%. That the gum was not pure was indicated not only by its appearance, but by the following fact.

About 20 mg. of the gum was placed in a porcelain crucible and strongly ignited. The material carbonized. After the carbon had burned away, and the crucible had cooled, one cc. of water was

added. The resulting solution was alkaline with respect to phenolphthalein.

The product of the experiment thus appears to have been ethyl 2,2-diethyl-3-ethyliminobutyrate instead of the desired ethyl 2,2-diethyl-3-iminobutyrate. Without checking the properties of the gum to make sure that the product suspected was actually obtained, attention was shifted to another alkylation procedure.

e. In a two necked flask fitted with a reflux condenser were placed approximately 25 cc. of anhydrous ether, and 2.4 g. (0.06 mole) of potassium metal. The condenser was fitted with a calcium chloride tube, and the system was so arranged that nitrogen could be blown out of the flask whenever it was necessary to introduce reagents thru the second neck of the flask. The reaction was carried out in an atmosphere of nitrogen. Ethyl 2-ethyl-3-iminobutyrate (10 g., 0.06 mole) was added to the mixture and a vigorous reaction ensued. As the reaction proceeded a yellow solid was precipitated. The mixture was gently refluxed for ninety minutes. At the end of that time all of the solid had gone into solution, and the potassium had completely disappeared. To the clear, deep yellow solution 10 g. (a slight excess) of ethyl iodide was added. A solid was at once precipitated with the evolution of a large quantity of heat. The mixture was refluxed for three hours and the ether solution was then recovered by rapid filtration. The ether was removed from the filtrate by distillation at 70 mm. pressure. The temperature of the heating bath was not permitted to rise above 72°. There was recovered, by this procedure, a deep orange viscous oil. It was placed in an evacuated desiccator over calcium chloride and Para-wax.

After a week had elapsed, the oil still showed no signs

of crystallization and it was decided to attempt distillation of the material at very low pressures. The material was sealed into a vacuum line that could be evacuated, with the aid of a mercury diffusion pump, to a pressure below 10^{-5} mm. At this pressure the oil was divided into four fractions. The oil was heated by placing a hot water bath around its container. It is necessary to emphasize the fact that the division into fractions was purely arbitrary. The fractions were so cut as to obtain four samples of about equal volume; a thermometer was sealed into the system, but at the pressure involved, even assuming that the boiling point can be defined, the rate of distillation is so low that the thermometer readings are completely valueless. The oil bumped rather badly during the distillation and as a result the first and second fractions were very slightly contaminated by some of the undistilled material.

A micro-Dumas nitrogen determination was carried out on the first and fourth fractions. The fourth fraction analyzed in the following fashion. N, 6.54%, 6.24%. The nitrogen value obtained for the first fraction was 6.64%. With so little difference between the two fractions it was deemed unnecessary to analyze the middle fractions. The analysis results indicate that again ethyl 2,2-diethyl-3-ethyliminobutyrate had been obtained. The nitrogen value calculated for that compound ($C_{12}H_{23}O_2N$), is 6.57%.

In order to prove that the compound obtained actually is the ethylimino compound as suspected, it was necessary to show the presence of the ethylimino group, and of a second ethyl group in the alpha position.

To ascertain whether or not the ethylimino group was present two or three micro drops of each of the fractions were hydro-

lyzed with hydrochloric acid, and the hydrolysis products subjected to the delicate carbylamine test. Each of the four fractions gave a strong positive carbylamine test; this proved that the ethylimino group was present in the molecule.

To show that a second ethyl group had been attached to the alpha carbon was not quite as simple a matter. The problem was solved in the following fashion: With respect to hydroxylamine the imino compounds behave in identically the same fashion as do the ketones. This being the case, ethyl 2,2-diethyl-3-ethyl-iminobutyrate should react with hydroxylamine under the proper circumstances to form 3-methyl-4,4-diethylisoxazol-5-one. It was found, by experiments performed with ethyl diethylacetoacetate, that the test could be applied to extremely small quantities of material.

A hydroxylamine reagent solution was prepared in the manner described under the preparation of the isoxazolone. To 0.5 cc. of this reagent in a 50 mm. test tube was added 1-2 drops of ethyl 2,2-diethylacetoacetate. A precipitate appeared at once. The solution was heated to the boiling point, and then placed in a centrifuge. The alcoholic reagent was decanted, and the solid washed by decantation with hot alcohol at least twice. To the solid was then added 0.5 cc. of water containing one drop of concentrated (18 molar) sulfuric acid. The acid solution was cooled to 0° before being added, and following its addition the mixture was immersed in an ice-salt bath. The decomposition of the sodium salt was complete in five minutes, and the isoxazolone produced by this procedure was collected on a microfilter. The isoxazolone produced in this way is extremely pure. It melts sharply at 40°-41°.

This test was applied to each of the four fractions obtained by distillation of the oil. Fractions one and three yielded

crystals which melted very sharply at 40° - 41° . Fraction two yielded crystals melting a little less sharply at 39° - 40.5° . So far as the material contained in these fractions is concerned, there is no question that a second ethyl group has been attached to the alpha carbon. The fourth fraction, though repeatedly tested, yielded no isoxazolone whatever. It is, therefore, not the compound suspected. After standing in stoppered test tubes for a period of a year, there is a vast amount of difference in both appearance and odor between the fourth fraction and the other three.

The physical properties of ethyl 2,2-diethyl-3-ethylimino-butyrate were not studied. The amount of time consumed by these investigations did not seem sufficiently to advance the synthesis of the desired pyrimidine to justify their continuance. The alkylation studies were, therefore, dropped.

10. Preparation of 1-phenyl-4-methyl-5-ethyluracil.--While the alkylation studies described above were being carried forward it was expected that ethyl 2,2-diethyl-3-iminobutyrate would be obtained. Since it was evident early in the experiments that physical separation of the latter compound from the reaction mixture would not be easily feasible some method of identifying the compound was sought. It seemed possible that phenyl isocyanate would react with the imino group and could, therefore, be used to characterize the compound. In order to study the reaction of such an imino group with phenyl isocyanate as well as to study the corresponding derivative of ethyl 2-ethyl-3-iminobutyrate the reaction of phenyl isocyanate with ethyl 2-ethyl-3-iminobutyrate was carried out in the following fashion. To 2.8 g. of ethyl 2-ethyl-3-iminobutyrate was added 2 g. of phenyl isocyanate. The reaction was carried out in an Erlenmeyer flask fitted with a calcium chloride tube in order to prevent the entrance of moisture. The mix-

ture was heated in a steam bath for a fifteen hour period and then cooled. After three hours, the oil first formed had become completely solid. The material so obtained was recrystallized from alcohol containing about 30 per cent of water. The compound so obtained melted at 74° - 76° .

It was suspected that this low melting solid was not the desired pyrimidine but rather the addition product of the imine and the phenyl isocyanate. The fact that the material was soluble in dilute alkali confirmed this assumption.¹

The addition of acid to the alkaline solution caused the precipitation of a white solid. This compound, after being repeatedly recrystallized from alcohol, in which it is but little soluble, and twice from hot water, melted at 284° corr.

The compound gave the following micro-analysis: Calculated for 1-phenyl-4-methyl-5-ethyluracil $C_{13}H_{14}N_2O$; N, 12.17%; C, 67.82%; H, 6.24%; found: N, 12.26%, 12.32%; C, 67.62%; H, 6.09%. This compound has not been previously reported.

The open chain compound first formed is readily soluble in alcohol, ether, chloroform, and carbon tetrachloride; it is slightly soluble in ligroin; it is insoluble in water. The pyrimidine is slightly soluble in hot alcohol and soluble in hot water; it is insoluble in cold water, alcohol, ether, chloroform, and carbon tetrachloride.

11. Preparation of 2-ethylacetoacetamide.--This compound was prepared in exactly the fashion described by H. Meyer.² A yield of about 33 per cent of the theoretical is obtained. The compound melts at 95° - 96° .

12. Preparation of 2,2-diethylacetoacetamide.--The method

¹Behrend and Roosen, Ann., 251, 238 (1889).

²H. Meyer, Monatshefte, 27, 1089 (1906).

of H. Meyer was employed in preparing this compound.¹ A yield of about 47 per cent of the theoretical is obtained in the reaction. The material melts at 122°-123°. It is soluble in hot water, alcohol, ether, chloroform, and carbon tetrachloride.

In order to determine whether the second ethyl group was attached to carbon or to nitrogen the following experiment was performed with the compound: About 20 mg. was placed in a 50 mm. test tube and heated with 0.5 cc. of molar hydrochloric acid. An oil separated as the material was heated. This was steam-distilled away as the solution was taken to dryness. To the water-soluble hydrolysis product which remained in the test tube was applied the carbylamine test. No trace of carbylamine could be detected. This indicates that the ethyl group is attached to the alpha carbon, and not to the nitrogen.

13. The preparation of N-2,2-diethylacetoacetyl-N'-phenyl-urea.--Phenyl isocyanate (2 g.) was sealed in a small bomb tube with 2.8 g. of 2,2-diethylacetoacetamide. The bomb was heated in a steam bath for about fifteen hours. It was not opened until twelve days after the heating was complete. The bomb contained a homogenous oil which solidified as it cooled. When the bomb was opened a gas was given off indicating that a pressure in excess of atmospheric had been built up during the course of the reaction. The solid was coated with a small amount of oily liquid; the odor of phenyl isocyanate was very marked, but this was to be expected inasmuch as an excess of phenyl isocyanate had been used.

The solid material was taken up in hot alcohol; as the alcohol cooled a very heavy precipitate appeared. It was separated and air dried. It melted at 75°-85°. It was recrystallized three

¹H. Meyer, Monatshefte, 28, 2 (1907).

times from alcohol; after the third recrystallization it melted at 85° - 89° , but it did not melt completely. It was possible to observe solid particles suspended in the melt. The material was examined under the microscope; two crystal forms were readily observed, flat, slightly, skewed square plates, and long fine needles.

Inasmuch as recrystallization from alcohol was not effecting a separation of the two solids present in the mixture the following procedure was employed. The mixture was taken up in a minimum of glacial acetic acid at a temperature below 40° . Water was added to this solution drop by drop until it showed the first signs of becoming cloudy. The solution was then gently heated until all cloudiness disappeared. The solution was then slowly cooled to the temperature of an ice-salt bath; a finely divided crystalline solid was precipitated. The solid was collected and recrystallized once from alcohol. The crystals so obtained melted sharply at 86.5° - 87.5° . Under the microscope only flat plates were found present.

The compound was subjected to micro-analysis. Calculated for N-2,2-diethylacetosetyl-N'-phenylurea ($C_{15}H_{20}O_3N_2$) N, 10.14%. Found: N, 10.14%, 9.95%.

The acetic acid filtrate was diluted with water; this caused the separation of an oil which slowly solidified. The solid was recrystallized from alcohol. Very pretty needles, melting sharply between 147° - 148° were obtained. It was suspected that they might be phenylurea, obtained by hydrolysis from the substituted acetylphenylurea. They were mixed with some phenylurea melting at 147° . The melting point of the mixture was lowered by twenty degrees. The identity of the solid was not further investigated.

14. Preparation of nitrourea.--Nitrourea was prepared from

urea nitrate by the method of Davis and Blanchard.¹

15. Attempt to prepare acylureas from acyl amides.--

a. To 2 g. (1 mole) of acetamide dissolved in 30 cc. of ethanol (95 per cent) was added 4.1 g. (1.15 moles) of nitrourea.² A small amount of sodium hydroxide was added to the mixture, and the mixture was refluxed over an electric hot plate. The nitrourea rapidly went into solution with the evolution of large quantities of gas. Refluxing was continued for 11 hours. While it was still hot the mixture was brought onto a filter and a small amount of insoluble material was recovered. This solid did not melt and was therefore discarded.

The alcoholic filtrate precipitated a crystalline solid as it cooled. This solid was recovered and recrystallized twice from alcohol and twice from water. Following this treatment, it melted sharply at 191°. Acetylurea melts at 217°-218°. The melting point of a mixture of the solid and acetylurea was determined. It melted at 176°-178° C.

The material was found to show the behaviour characteristic of ethyl allophanate,³ whose melting point is 191°. The nitrogen content of the solid was determined. Calculated for ethyl allophanate N, 21.20%. Found: N, 21.24%, 21.35%. This leaves no question as to the identity of the solid recovered. No acetylurea could be recovered from the filtrate from which the ethyl allophanate had been separated.

b. Acetamide (1 g.) was mixed with 2 g. of nitrourea and the mixture heated at the temperature of refluxing ethanol for a period

¹Op. cit.

²The method employed is that of Buck and Terry, op. cit.

³Mulliken, "The Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, 1916, II, 207.

of about 15 hours. The mixture formed a perfectly homogenous melt with the evolution of a large quantity of gas. As the heating continued, a solid separated out in the melt. When the heating was discontinued the melt solidified completely.

The solid was taken up in hot water. As the solution cooled, a crystalline solid was precipitated. It did not melt, but it did sublime above 360° . It was identified as cyanuric acid by its copper salt.¹ No acetylurea could be recovered from the filtrate.

c. The experiment described in (a) above was repeated with 2,2-diethylacetoacetamide instead of acetamide. The 2,2-diethylacetoacetamide was recovered unchanged.

d. One gram of 2,2-diethylacetoacetamide was dissolved in 40 cc. of water. To this solution was added 0.344 g. of potassium cyanate. A solution of 1.33 cc. of 6N. hydrochloric acid dissolved in 50 cc. of water was then added dropwise over a period of two hours. The solution was left undisturbed over night. The next morning it was evaporated to 20 cc. and cooled. The amide, melting at 121° - 122° was recovered.

e. To 20 cc. of an almost saturated solution of potassium cyanate was added approximately 0.5 grams of 2,2-diethylacetoacetamide. The amide went into solution as the mixture was warmed. The solution was refluxed for about three hours. During the early part of the refluxing period large amounts of ammonia gas were liberated. An oil appeared to separate most of which disappeared, as the refluxing continued, and a small amount of sublimate condensed on the walls of the condenser. After refluxing was stopped a large quantity of solid separated from the cooling solution. It

¹Ibid., p. 84.

was separated from the liquid by filtration, and air dried. It was repeatedly extracted with ether. The ether solution was evaporated to dryness and the solid so obtained was recrystallized from hot water. White needles, melting at 121° - 122° were recovered. Mixing the solid with 2,2-diethylacetoacetamide did not lower the melting point. The amount of amide recovered was very closely equal to the amount originally used.

16. Attempts to prepare 2 ethoxy-4-methyl-5,5-diethyl-6-oxypyrimidine from ethyl isourea.--

a. Because ethyl 2,2-diethylacetoacetate so readily formed a ring compound under the conditions employed in preparing the isoxazolone an experiment was performed, applying the same condition to the reaction of the ester with ethyl isourea.¹

To 15 cc. of absolute alcohol was added 1.9 g. of sodium. After the sodium had completely dissolved 4.2 g. of ethyl-isourea hydrochloride was added to the solution and the mixture refluxed for about two and one half hours. It was then filtered, and to the filtrate was added 5 g. of ethyl 2,2-diethylacetoacetate. The solution was refluxed for three hours. Ten minutes after refluxing was commenced a dense white precipitate appeared in the reaction vessel. The mixture was brought onto a filter and the solid was recovered. The solid was readily decomposed in dilute acid; the decomposition produced the evolution of a gas, and the separation of an oil which would neither crystallize or solidify. Its odor was typical of unsymmetrical diethylacetone. No solid product could be obtained from the reaction mixture, other than the oil just described. From its reactions it may be safely inferred

¹J. Stieglitz, and R. H. McKee, Ber., 33, 1517 (1901); R. H. McKee, Am. Chem. J., 26, 255 (1901). The method of W. L. Terre, was used. Master's Dissertation, University of Chicago, (1932).

that the solid is the sodium salt of 2,2-diethylacetoacetic acid.

b. The method employed by Dr. Lowe in preparing 2-ethoxy-4-methyl-5-ethyl-6-oxypyrimidine was applied to ethyl 2,2-diethyl-3-oximinobutyrate.

To 2 g. of ethyl 2,2-diethyl-3-oximinobutyrate was added 2 g. of ethyl isocourea. The mixture was warmed in order to melt the oxime, and placed in vacuo over potassium hydroxide, concentrated sulfuric acid, and calcium chloride. Crystals began to appear in the reaction mixture at the end of twenty-four hours. On the second day the potassium hydroxide and sulfuric acid were changed.

After having been four days in vacuo the material was removed from the desiccator. It was light yellow in color. Approximately 15 cc. of ether was added to it; a white solid separated which was washed twice with anhydrous ether by decantation and then brought onto a filter.

The solid thus obtained was identified, by analysis, as consisting, in all probability of a mixture of cyanuric acid amids. Its nitrogen content was determined as: N, 61.72%, 62.03%.

The ethereal filtrate was gently heated over a hot plate until all of the ether was removed. The residual oil was cooled, and seeded with a crystal of the oxime. It at once crystallized. Recrystallized from alcohol, the solid obtained melted between 55°-56°; it was mixed with the oxime, melting at 55°-56°; the melting point was unchanged. The starting compound had been recovered.

Summary

1. The objective of this investigation was the synthesis of 4-methyl-5,5-diethyluracil.

2. The path which suggests itself, the direct condensation of ethyl 2,2-diethylacetoacetate with urea, or a urea derivative, having been found blocked, presumably by stereochemical interferences, three other paths of synthetic approach were studied.

3. The first line of attack was thru the attempted reduction of ethyl 2,2-diethyl-3-oximinobutyrate to ethyl 2,2-diethyl-3-aminobutyrate, which, if formed should be convertible into ethyl 2,2-diethyl-3-ureidobutyrate and then to the desired uracil. The preparation of the oxime was greatly improved, and during the course of this work the study of, and preparation of, 3-methyl-4,4-diethylisoxazol-5-one, a substance first obtained in the course of the preparation of the oxime, was carried out. The attempted reduction of the oxime to the amine was not successful.

4. The alkylation of ethyl 2-ethyl-3-iminobutyrate was carried out with the object of condensing ethyl 2,2-diethyl-3-iminobutyrate if formed, with cyanic acid, and of converting the condensation product into the desired uracil. The imino group, as well as the 2-carbon atom, was alkylated, forming ethyl 2,2-diethyl-3-ethyliminobutyrate. The investigation was not pursued. The presence of the N-ethyl group blocks urea formation.

5. To test the possibility of urea formation thru an imino group the reaction between phenyl isocyanate and ethyl 2-ethyl-3-iminobutyrate was studied. The reaction led to the formation of 1-phenyl-4-methyl-5,5-diethyluracil, thus showing that the method of attack planned was entirely feasible in the absence of blocking groups.

6. The third line of approach aimed at the conversion of 2,2-diethylacetoacetamide into 2,2-diethylacetoacetylurea. The amid was found to react with phenyl isocyanate, forming N-2,2-diethylacetoacetyl-N'-phenylurea. However, all attempts to convert the amid into 2,2-diethylacetoacetylurea were unsuccessful.

7. It was shown that ethyl isourea would not react with ethyl 2,2-diethyl-3-oximinobutyrate, nor with ethyl 2,2-diethylacetoacetate in basic alcohol solution to give 2-ethoxy-4-methyl-5,5-diethyl-6-oxypyrimidine, an ethoxy derivative of the desired uracil.

8. While the main objective, the synthesis of 4-methyl-5,5-diethyluracil was not attained, it is believed that the results clear the way to further promising approaches.

